

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing: 07 December 2000 (07.12.00)	
International application No.: PCT/US00/14829	Applicant's or agent's file reference: 15280-3951PC
International filing date: 26 May 2000 (26.05.00)	Priority date: 27 May 1999 (27.05.99)
Applicant: PASTAN, Ira et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International preliminary Examining Authority on:
21 September 2000 (21.09.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer: J. Zahra Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 15280-3951PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/14829	International filing date (day/month/year) 26/05/2000	Priority date (day/month/year) 27/05/1999
International Patent Classification (IPC) or national classification and IPC C07K16/00		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 21/09/2000	Date of completion of this report 06.08.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Montrone, M Telephone No. +49 89 2399 8711 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/14829

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-54 as originally filed

Claims, No.:

1-50 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

Sequence listing part of the description, pages:

1-5, filed with the letter of 14.08.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/14829

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-5,8,10,12-16,21,27,31,33-40.

because:

- ☒ the said international application, or the said claims Nos. 33-40 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-5,8,10,12-16,21,27,31,33,34.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/14829

1. Statement

Novelty (N)	Yes:	Claims	6,7,9,11,17-20,22-26,28-30,32,35-40
	No:	Claims	41-50
Inventive step (IS)	Yes:	Claims	6,7,9,11,17-20,22-26,28-30,32,35-40
	No:	Claims	41-50
Industrial applicability (IA)	Yes:	Claims	1-32,41-50
	No:	Claims	

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Reference is made to the following documents:

- D1: Immunotechnolgy, vol. 2, p.: 169-179 (1996)
- D2: PNAS, vol. 95, p.: 6037-6042 (1998)
- D3: PNAS, vol. 95, p.: 669-674 (1998)

Item III:

No opinion will be formulated for the patentability of the subject-matter of claims 1-5, 8, 10, 12-16, 21, 27, 31, 33 and 34 since a search report has not been established for these claims.

In addition, claims 33 to 40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(i) PCT).

Item V:

1. Claim 41 refers to a method for identifying a polypeptide which has a higher affinity for a target antigen than does a parental antibody.

D1 discloses a phage selection method which allows the selection of polypeptides having an increased affinity in comparison to their parental polypeptides (see page 172, left col., to right col., first para.).

In addition, D1 discloses a phage library having encoded different VH domains. Site specific randomisation in either CDR1 or CDR2 is carried out. In CDR1 the randomisation was performed on three residues (31, 33, 35) which were known to be the most variable in said domain. It is considered that these residues are encoded by hot spot codons due to their high natural variability. The same applies to the three residues being randomised in the CDR2 domain, which are located in the centre of a region containing the most variable residues (see page 173, right col., second para. to page 174, left col., first para.). Due to this approach, the libraries are kept at a

relative small size (see page 174, left col., second para.). Thus, D1 is considered to be detrimental to the novelty of claims 41 to 48.

D2 discloses a stepwise in vitro affinity maturation of Vitaxin, a humanised mAB. The maturation was carried out by single mutations of all 20 amino acids at each CDR residue, resulting in the expression of 2336 unique clones. The affinity was increased by a factor of up to 90 fold (see abstract, page 6039, left col., first para.; page 6042, left col., third to fifth para.). An ELISA was carried out to test the relative affinities of the different antibodies constructed (see page 6040, left col., first para.). Thus, D2 is considered to be detrimental to the novelty of the subject-matter of claims 41 to 46 and 48 to 50.

Consequently, the subject-matter of claims 41 to 50 is not considered to be novel and does not comply with the provisions of Art. 33(2) PCT.

2. However, the subject-matter of claim 6 is considered to be novel and inventive and might therefore serve as basis for a new and allowable independent claim 1.

D3 discloses the antimesothelin antibody SS as referred to in claim 6 (see abstract, page 670, left col., third para., page 671, right col., first para.). However, an antimesothelin antibody SS having at least one amino acid substitution at the position S92, G93 or Y94 is not disclosed in said document. Thus, the subject-matter of said claim is novel over D3 (Art. 33(2) PCT). The same applies for the subject-matter of claims 7, 9, 11, 17 to 20, 22 to 26, 28 to 30, 32 and 35 to 40. Moreover, there is no indication given in D3 that said substitution would result in an increase in binding affinity of at least an factor 5 in comparison to the parental antibody. Since this cannot be deduced from D3 alone or in combination with any other available document, the presence of an inventive step can be acknowledged for the subject-matter of claim 6 (Art. 33(3) PCT). The same applies for the subject-matter of claims 7, 9, 11, 17 to 20, 22 to 26, 28 to 30, 32 and 35 to 40.

3. For the assessment of the present claims 33 to 40 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/14829

compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI:

The document "Nature Biotechnology, vol. 17, p. 568-572 (1999)" published in June 1999 could be relevant to the subject-matter of the present application if the priority of the claims is not valid.

Item VII:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in documents D1 or D2 is not mentioned in the description, nor are these documents identified therein.

Item VIII:

The scope of claim 46 is unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 15280-3951PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/14829	International filing date (day/month/year) 26/05/2000	(Earliest) Priority Date (day/month/year) 27/05/1999
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1
☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/14829

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 33 to 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-5, 8, 10, 12-16, 21, 27, 31, 33, 34
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5, 8, 10, 12-16, 21, 27, 31, 33, 34

Present claims 1-5, 8, 10, 12-16, 21, 27, 31, 33, 34 relate to a product defined by reference to a desirable characteristic or property, namely "having at least 5 times higher binding affinity for an antigen than does a parental antibody."

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products of claims 6, 22, 28, 30 and claim 35 which relates to a method of killing malignant cells with the antibodies of claims 6 and 22.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/14829

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K16/00 A61K39/395 //C07K16/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, WPI Data, EPO-Internal, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAVIES JULIAN ET AL: "Affinity improvement of single antibody VH domains: Residues in all three hypervariable regions affect antigen binding." IMMUNOTECHNOLOGY (AMSTERDAM), vol. 2, no. 3, 1996, pages 169-179, XP004070292 ISSN: 1380-2933 abstract page 173, column 2, paragraph 2 -page 173, column 1, paragraph 2 page 178, column 1, paragraph 3 --- -/--	41-48

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

17 October 2000

Date of mailing of the international search report

27. 10. 00

Name and mailing address of the ISA

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Authorized officer

Montrone, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/14829

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WU HERREN ET AL: "Stepwise in vitro affinity maturation of Vitaxin, an alphavbeta3-specific humanized mAb." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 11, 26 May 1998 (1998-05-26), pages 6037-6042, XP000918969 May 26, 1998 ISSN: 0027-8424 abstract page 6037, column 2, paragraph 4 page 6038, column 1, paragraph 2 page 6038, column 2, paragraph 8 -page 6039, column 2, paragraph 1 page 6039, column 2, paragraph 2 page 6040, column 1, paragraph 2 -column 2, paragraph 1 page 6042, column 1, paragraph 3 - paragraph 5</p> <p>---</p>	41-46, 48-50
A	<p>CHOWDHURY PARTHA S ET AL: "Isolation of a high-affinity stable single-chain Fv specific for mesothelin from DNA-immunized mice by phage display and construction of a recombinant immunotoxin with anti-tumor activity." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 2, 20 January 1998 (1998-01-20), pages 669-674, XP002102004 Jan. 20, 1998 ISSN: 0027-8424 cited in the application abstract page 670, column 1, paragraph 3 page 671, column 1, paragraph 4 page 671, column 2, paragraph 1</p> <p>---</p>	6,7,9, 11, 17-20, 22-26, 28-30, 32,35-50
A	<p>GREEN NANCY S ET AL: "Somatic hypermutation of antibody genes: A hot spot warms up." BIOESSAYS, vol. 20, no. 3, March 1998 (1998-03), pages 227-234, XP000940929 ISSN: 0265-9247 abstract page 231, column 2, paragraph 2 -page 232, column 1, paragraph 1</p> <p>---</p> <p style="text-align: center;">-/--</p>	42,44,47

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/14829

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DORNER T. ET AL.: "Delineation of selective influences shaping the mutated expressed human Ig heavy chain repertoire" J. IMMUNOL., vol. 160, no. 6, 1998, pages 2831-2841, XP000918992 abstract page 2831, column 2, paragraph 1 page 2835, column 2, paragraph 1 -page 2836, column 1, paragraph 3 page 2837, column 1, paragraph 2 page 2839, column 1, paragraph 4 -column 2, paragraph 2 -----	41,42, 46-50
P,X	CHOWDHURY P. ET AL.: "Improving antibody affinity by mimicking somatic hypermutation in vitro" NATURE BIOTECHNOLOGY, vol. 17, June 1999 (1999-06), pages 568--572, XP000918985 abstract page 568, column 2, paragraph 1 - paragraph 3 page 569; figure 1; table 1 page 570, column 1, paragraph 4 page 571, column 1, paragraph 2 - paragraph 4 -----	6,7,9, 11, 17-20, 22-26, 28-30, 32,35-50